Appendix A
(marked-up versions of substitute paragraphs)

(**marked-up version** corresponding to the four (4) contiguous paragraphs beginning on page 2, line 28 and extending through page 3, line 21)

Therefore, there is a need in the art to find molecules that bind to cellular HER-2 and particularly molecules that bind to different sites than humanized antibodies to HER-2 (*e.g.*, [Herceptin®] HERCEPTIN®). Such molecules would be useful therapeutic agents for various cancers that overexpress HER-2.

Summary of the Invention

The present invention provides an isolated polypeptide having from about 50 to 79 amino acids taken from the sequence of SEQ ID NO. 1, wherein the polypeptide binds to the extracellular domain ECD of HER-2 at an affinity of at least 10^8. Preferably, the isolated polypeptide is from about 69 to 79 amino acids in length. Preferably, the isolated polypeptide binds to a site on the ECD of HER-2 that is different from the site of binding of [Herceptin®] HERCEPTIN® (a marketed humanized monoclonal antibody that is used for the treatment of cancer and that binds to the ECD or HER-2).

The present invention further provides an isolated DNA sequence that codes on expression for a polypeptide having from about 50 to 79 amino acids taken from the sequence of SEQ ID NO. 1, wherein the polypeptide binds to the extracellular domain ECD of HER-2 at an affinity of at least 10^8. Preferably, the isolated polypeptide is from about 69 to 79 amino acids in length. Preferably, the isolated polypeptide binds to a site on the ECD of HER-2 that is different from the site of binding of [Herceptin] HERCEPTIN® (a marketed humanized monoclonal antibody that is used for the treatment of cancer and that binds to the ECD or HER-2). The present invention further provides a transfected cell comprising an expression vector having a DNA sequence that codes on expression for a polypeptide having from about 50 to 79 amino acids taken from the sequence of SEQ ID NO. 1, wherein the polypeptide binds to the extracellular domain ECD of HER-2 at an affinity of at least 10^8.

The present invention further provides an isolated and glycosylated polypeptide having from about 80 to 419 amino acids taken from the sequence of SEQ ID NO. 2, wherein the C terminal 79 amino acids are present, and wherein at least three N-linked glycosylation sites are present. Preferably, the isolated polypeptide is from about 350 to 419 amino acids in length and four N-linked glycosylation sites are present. Preferably, the isolated polypeptide binds to a site on the ECD of HER-2 that is different from the site of binding of [Herceptin] HERCEPTIN® (a marketed humanized monoclonal antibody that is used for the treatment of cancer and that binds to the ECD or HER-2).

(**marked-up version** for the paragraph beginning on page 4, line 24 through line 32)

The present invention further provides a method for targeting a therapeutic agent to solid tumor tissue, wherein the solid tumor tissue is characterized by overexpression of HER-2, comprising attaching the therapeutic agent to an isolated polypeptide having from about 50 to 79 amino acids taken from the sequence of SEQ ID NO. 1, wherein the polypeptide binds to the extracellular domain ECD of HER-2 at an affinity of at least 10^8. Preferably, the isolated polypeptide is from about 69 to 79 amino acids in length. Preferably, the isolated polypeptide binds to a site on the ECD of HER-2 that is different from the site of binding of [Herceptin®] HERCEPTIN® (a marketed humanized monoclonal antibody that is used for the treatment of cancer and that binds to the ECD or HER-2).

(**marked-up version** for the paragraph beginning on page 5, line 27 and extending through line 33)

Figure 2 shows the detection of alternative HER-2 transcripts containing the ECDIIIa sequence by Northern blot analysis. PolyA+ mRNA (2.5 μg) from different human fetal tissues (Clontech) or isolated from HEK-293 cells was resolved in a formalin agarose gel and transferred to a [BrightStar®] BRIGHTSTAR® membrane (Ambion) in 10xSSC. The membrane was hybridized with a ^{32}P-labeled antisense RNA probe complimentary to the ECDIII sequence, stripped and reprobed with a ^{32}P labeled cDNA probe specific for the 5' HER-2 exon sequence. The membranes were washed under high stringency conditions and analyzed by phosphorimaging (Molecular Dynamics).

(**marked-up version** for the paragraph beginning on page 12, line 8 and extending through line 20)

The present invention further provides a method for targeting a therapeutic agent to solid tumor tissue, wherein the solid tumor tissue is characterized by overexpression of HER-2, comprising attaching the therapeutic agent to an isolated polypeptide having from about 50 to 79 amino acids taken from the sequence of SEQ ID NO. 1, wherein the polypeptide binds to the extracellular domain ECD of HER-2 at an affinity of at least 10^8. Preferably, the isolated polypeptide is from about 69 to 79 amino acids in length. Preferably, the isolated polypeptide binds to a site on the ECD of HER-2 that is different from the site of binding of [Herceptin®] HERCEPTIN® (a marketed humanized monoclonal antibody that is used for the treatment of cancer and that binds to the ECD of HER-2). It was discovered that the 79 amino acid polypeptide [SEQ ID NO. 1] exhibited surprising high affinity binding properties to the ECD of HER-2. Moreover,

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the site of such binding is different and unaffected by the site of binding of a marketed humanized monoclonal antibody ([Herceptin®] HERCEPTIN®). Therefore, the high binding affinity enables the 79 amino acid polypeptide to function as a targeting molecule to tumor cells expressing HER-2.